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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,994	02/27/2001	Edmonds Taylor Brian	X-12239	6826

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,994	BRIAN, EDMONDS TAYLOR	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-47* is/are pending in the application.

4a) Of the above claim(s) *37 and 39-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *200402* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 32-47 are pending.

Applicant's election with traverse of group I and the species SEQ ID NO: 2 in the paper filed 10/29/2003 is acknowledged. The traversal is on the ground(s) that SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6 form a single inventive concept and that it is improper to restrict out members of a Markush group that share a common utility and a substantial structural feature. This is not found persuasive because the claims are directed to a hLTBP-3 polypeptide comprising at least 181 contiguous amino acids of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6. SEQ ID NO: 2 and SEQ ID NO: 6 are 1208 and 1257, respectively, amino acids long. SEQ ID NO: 2 contains a 49 amino acid deletion with respect to SEQ ID NO: 6. SEQ ID NO: 4 is 188 amino acids long and is identical to the most N-terminal 188 amino acids of SEQ ID NO: 6. SEQ ID NO: 4 is identical to the most N-terminal 172 amino acids of SEQ ID NO: 6 and comprises additional residues that are in SEQ ID NO: 6 but not in SEQ ID NO: 2. The claims do not require that the genus of polypeptides comprise the same 181 contiguous amino acids. Accordingly, 181 contiguous amino acids of SEQ ID NO: 2 would not necessarily overlap and share the same technical feature with SEQ ID NO: 4 or SEQ ID NO: 6. Nevertheless, the examiner agrees without prejudice to rejoin SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6 for examination in claim 32 as it now stands.

The requirement is still deemed proper and is therefore made FINAL.

Claims 37, 39-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 10/29/2003.

Applicant's request to rejoin group III (claims 40 and 43) is acknowledged. In accordance with the Official Gazette notice dated March 26, 1996 (1184 O.G. 86) process claims 40 and 43, which do not depend from or otherwise include all the limitations of the allowable product, have NOT been rejoined.

Information Disclosure Statement

The information disclosure statement filed 01/29/2002 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

Claims 32, 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a salt of an hLTBP-3 polypeptide, does not reasonably provide enablement for a pharmaceutically acceptable salt of an hLTBP-3 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass a pharmaceutically acceptable salt of a hLTBP-3 polypeptide. The terms "pharmaceutical" and/or "pharmaceutically" encompass and/or imply preventing, diagnosing, alleviating, treating, or curing a disease or condition in a mammal.

The specification contains the following disclosures regarding the activity of hLTBP-3:

> There is convincing evidence that the secreted LTBP proteins bind latent growth factors, namely TGF-βs, intracellularly and facilitate their folding and secretion to proper extracellular matrix storage sites. It has also been suggested that LTBPS protect the small latent complexes from proteolytic activity which governs the activation of latent complexes. Page 2, full paragraph 2.
>
> The hLTBP-3 gene of the present invention encodes a protein that is the human homolog of the mouse latent transforming growth factor-β binding protein-3 gene. These proteins are often co-expressed with TGF-βs and appear to modulate the activation process of TGF-βs. Thus, the hLTBP genes and their protein products are useful for modulating the activity of TGF-β. Paragraph bridging pages 13-14.
>
> hLTBP-3 functionality is easily tested, for example, in an assay that measures the ability to inhibit cell proliferation. Page 17, last full paragraph.
>
> In addition, use of antagonists of TGF-β may form the basis of important novel approaches for the treatment of a large spectrum of serious chronic conditions in which excessive TGF-β action appears to be responsible for tissue damage caused by scarring. Thus, hLTBP-3 can be used as a potent and specific inhibitor of TGF-β for the prevention of fibrotic conditions. Page 38, full paragraph 2.
>
> The effect of hLTBP-3 on reversing inhibition of cell growth induced by TGF-β can be assessed in various cell lines including, but not limited to, the MvlLu cell line. Page 45, full paragraph 2.
>
> hLTBP-3 expression is expected to inhibit TGF-β promoters and the secretion of TGF-β. Page 51, last full paragraph.

Although working examples are not required, they are a factor to be considered. The present specification contains no working examples of the modulation of TGF-β activity with the exogenous administration of hLTBP-3. Although the secreted LTBP proteins bind latent growth

factors, namely TGF-βs, intracellularly and facilitate their folding and secretion to proper extracellular matrix storage sites (specification at page 2, full paragraph 2), there is no evidence of record that the addition of exogenous hLTBP-3 binds TGF-β extracellularly and modulates the activity of TGF-β in any way. Furthermore, Yin (U) discloses that the LTBP-3 gene is co-expressed with TGF-β (Abstract). LTBP is linked by a disulfide bond to LAP (page 10147, right column, first full paragraph). LTBP-1, LTBP-2, and LTBP-3 may contribute to the regulation of extracellular matrix production by facilitating the assembly and secretion of large latent growth factor complexes and *then* targeting the complex to specific connective tissues (page 10159, right column, last sentence) (emphasis added). There is nothing in the prior art of record teaching the skilled artisan how to bind TGF-β with an exogenous source of LTBP-3.

It is noted that claims 40 and 43 achieve opposite results with the administration of identical compositions. The present specification lacks guidance for, and working examples of, achieving one result to the exclusion of the other. In other words, the present specification lacks guidance for blocking the result of claim 43 (stimulating tissue growth) when the result of claim 40 (inhibiting tissue growth) is to be achieved and lacks guidance for blocking the result of claim 40 (inhibiting tissue growth) when the result of claim 43 (stimulating tissue growth) is to be achieved.

While a specification need not disclose what is well known in the art, that rule does not excuse an applicant from providing a complete disclosure. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. It is the additional characterization of the claimed hLTBP-3 that

is required in order to practice the invention commensurate in scope with the claims that constitutes undue experimentation.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Claims 32-36, 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to or encompass a "hLTBP-3" polypeptide comprising at least 181 contiguous amino acids of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6. SEQ ID NO: 2 and SEQ ID NO: 6 are 1208 and 1257, respectively, amino acids long. SEQ ID NO: 2 contains a 49 amino acid deletion with respect to SEQ ID NO: 6. SEQ ID NO: 4 is 188 amino acids long and is identical to the most N-terminal 188 amino acids of SEQ ID NO: 6. SEQ ID NO: 4 is identical to the most N-terminal 172 amino acids of SEQ ID NO: 6 and comprises additional residues that are in SEQ ID NO: 6 but not in SEQ ID NO: 2.

The following passages from the specification seem to be the most relevant for construing the claim:

> The present invention provides novel human TGF-β latent binding protein-related nucleic acid molecules, their encoded polypeptides, pharmaceutical compositions comprising same, and therapeutic uses thereof. Page 3, full paragraph 1.
>
> The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding nucleic specific hLTBP-3 polypeptides, hLTBP-3 polypeptide

> fragments, as well as variants comprising at least one domain thereof. Page 3, full paragraph 2.
>
> A hLTBP-3 polypeptide of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. Paragraph bridging pages 15-16.
>
> Non-limiting mutants that can enhance, decrease, or maintain at least one of the listed activities are contemplated. Paragraph bridging pages 16-17.
>
> Also contemplated by the present invention are proteins that are functionally related to hLTBP-3. Page 17, full paragraph 1.

When the claims are read in light of the specification the intended scope of the term "hLTBP-3 polypeptide" becomes unclear. The metes and bounds are not clearly set forth.

Claims 32-36, 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass a "hLTBP-3" polypeptide comprising at least 181 contiguous amino acids of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6. SEQ ID NO: 2 and SEQ ID NO: 6 are 1208 and 1257, respectively, amino acids long. SEQ ID NO: 2 contains a 49 amino acid deletion with respect to SEQ ID NO: 6. SEQ ID NO: 4 is 188 amino acids long and is identical to the most N-terminal 188 amino acids of SEQ ID NO: 6. SEQ ID NO: 4 is identical to the most N-terminal 172 amino acids of SEQ ID NO: 6 and comprises additional residues that are in SEQ ID NO: 6 but not in SEQ ID NO: 2.

The following passages from the specification seem to be the most relevant for construing the claim:

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>
> The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding nucleic specific hLTBP-3 polypeptides, hLTBP-3 polypeptide fragments, as well as variants comprising at least one domain thereof. Page 3, full paragraph 2.
>
> A hLTBP-3 polypeptide of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. Paragraph bridging pages 15-16.
>
> Non-limiting mutants that can enhance, decrease, or maintain at least one of the listed activities are contemplated. Paragraph bridging pages 16-17.
>
> Also contemplated by the present invention are proteins that are functionally related to hLTBP-3. Page 17, full paragraph 1.

This is a genus claim. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common functional attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the

omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a "hLTBP-3" polypeptide comprising at least 181 contiguous amino acids of SEQ ID NO: 2, SEQ ID NO: 4, or SEQ ID NO: 6 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-36, 38 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over nucleic acids, proteins, and cells as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or 'Purified" as taught by pages 10 and 13 of the specification. See MPEP 2105.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (571) 272-0887.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
FEBRUARY 13, 2004